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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,877	08/02/2001	Jerry Y. Jonn	104226.01	4857
45473	7590	07/21/2005	EXAMINER	
HUTCHISON & MASON PLLC			CHOI, FRANK I	
PO BOX 31686			ART UNIT	
RALEIGH, NC 27612			PAPER NUMBER	

1616

DATE MAILED: 07/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/919,877

Applicant(s)

JONN ET AL.

Examiner

Frank I. Choi

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 4/4/2005.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-27,46,48-71 and 73 is/are pending in the application.
- 4a) Of the above claim(s) 18-27,46 and 48-58 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-17,59-71 and 73 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3-16, 59-71, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (US Pat. 5,981,621) in view of Kronenthal et al. (US Pat. 3,995,641), Hammerslag (US Pat. 6,386,203) and EP 0 965 623.

Clark et al. teach a composition comprising at least two different monomers which form a medically acceptable polymer, at least one plasticizer and a mixture of anionic and radical stabilizers, such as sulfur dioxide, hydroquinone, p-methoxyphenol and butylated hydroxyanisole (Column 2, lines 63-68, Columns 3-6, Claims 1, 7). It is taught that in applying composition a polymerization initiator, such as benzalkonium chloride, is used and may be readily selected by one of ordinary skill in the art without undue experimentation (Column 11, lines 18-68). Examples of suitable monomers include 2-octyl cyanoacrylate, 2-isopropoxyethyl cyanoacrylate and alpha-cyanoacrylates disclosed in US Pat. 3,995,641 to Kronenthal et al. (Column 4, lines 7-68, Column 5, lines 1-65)

Kronenthal et al. teaches carbalkoxyalkyl 2- cyanoacrylates which are readily assimilated by tissues and exhibit a relatively low degree of inflammatory tissue response (column 1, lines 60-68, Column 2, lines 1-11). It is disclosed that carbalkoxyalkyl 2-cyanoacrylates (0%, 25%,

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17%, 26% polymer remaining after 16 weeks) biodegraded at a faster rate than isobutyl 2-cyanoacrylate (82% remaining after 16 weeks) (Column 13, lines 1-30).

Hammerslag teaches that polymerizable cyanoacrylates can be co-polymerized with other compounds that alter elasticity, modify viscosity and aid in biodegradation (Column 5, lines 21-33). It is taught that suitable cyanoacrylates can be chosen from methyl, ethyl, butyl, methoxypropyl, alkoxyalkyl, and carbalkoxyalkyl depending on acceptable toxicity and other properties for a given application (Column 5, lines 54-67). It is taught that there is a wide variation in the rates of biodegradation of cyanocrylates but generally polymers of cyanoacrylates which have substituents that are small and/or contain one or more oxygen-containing functional groups appear to have increased biodegradability rates whereas cyanoacrylates having long chain alkyl groups lacking in oxygen-containing functional groups as substituents tend to form polymers which biodegrade more slowly (Column 6, lines 33-45). It is taught that one of ordinary skill in the art would be able to by routine experimentation choose a cyanoacrylate with suitable biodegradation characteristics (Column 6, lines 49-56).

EP 0 965 623 teaches the combination of sulfuric acid and sulfur dioxide with free radical stabilizers for use in cyanoacrylate compositions to stabilize and enhance the shelf-life of said composition (Pg. 4, lines 5-35, Pg. 5, lines 33-51). It is taught that suitable cyanoacrylates include 2-octyl cyanocrylate, 2-isopropoxyethyl cyanoacrylate and alpha-cyanoacrylates disclosed in US Pat. 3,995,641 to Kronenthal et al. (Pg. 9, Pg. 10, lines 1-28).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose a composition or film having a first monomer, which includes alkyl ester cyanocrylate, and a different second monomer where the absorption rate of the first monomer

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species is different from the absorption rate of the second monomer species. However, the prior art amply suggests the same as the prior art discloses the combination of different monomers in forming medical adhesives. Further, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine an alkyl ester cyanoacrylate with a different cyanoacrylate, such as an octyl 2-cyanoacrylate or alkylether cyanoacrylate, with the expectation that biodegradation of the composition could be adjusted readily by modifying the ratio of the monomers and the composition would have a low degree of inflammatory response. Further, one of ordinary skill in the art would have been motivated to combine sulfur dioxide and sulfuric acid with radical stabilizers such as hydroquinone, p-methoxyphenol and butylated hydroxyanisole with the expectation that the composition would be more stable. Finally, one of ordinary skill in the art would have been motivated to use benzalkonium chloride with the expectation that it would act as a polymerization initiator.

Examiner has duly considered Applicant's arguments but deems them unpersuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 231 USPQ 375 (Fed. Cir. 1986). Further, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 208 USPQ 871 (CCPA 1981).

Contrary to Applicant's arguments, the combined teachings of the prior art disclose or suggested the claimed invention as recited in claim 1 and claim 59.

As acknowledged by Applicant, Clark et al. specifically discloses the combination of at least two different monomers (See Clark et al. at claim 7). Applicant argues that Hammerslag teaches away from the claimed invention because it discloses that cyanoacrylates may be combined with other compounds that may aid biodegradation. However, this is not a teaching away from the claimed invention. Hammerslag does not specifically exclude mixtures of cyanoacrylate polymers. One of ordinary skill in the art knowing that other compounds can be combined with cyanoacrylates to aid biodegradation and knowing that different cyanoacrylates have different biodegradation rates would expect that mixtures of two different cyanoacrylates having different biodegradation rates would result in a polymer having an intermediate biodegradation rate. Further, Kronenthal et al discloses methods of testing the biodegradation rate of cyanoacrylates and that alkyl 2-cyanoacrylates, except for methyl, have biodegradation rates which are substantially slower than the carbalalkoxy 2-cyanoacrylates. As such, combination of carbalalkoxy 2-cyanoacrylates with alkyl 2-cyanoacrylates will be the combination of cyanoacrylates having at least a 10% difference in absorption rates. Further, in light of the above, the biodegradation rate can be readily determined with respect to other cyanoacrylates which can be combined with alkyl 2-cyanoacrylates as desired to achieve the appropriate biodegradation rate including cyanoacrylates having biodegradation rates greater than 10% of the alkyl 2-cyanoacrylates. Further, contrary to Applicant's arguments one of ordinary skill in the art would have been motivated to combine the above with a benzalkonium

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chloride, i.e. a quaternary amine, with the expectation that it will act as a polymerization initiator.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Claims 1, 3-16, 59-71, 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Clark et al. (US Pat. 5,981,621) in view of Kronenthal et al. (US Pat. 3,995,641), Hammerslag (US Pat. 6,386,203) and EP 0 965 623, in further view of Banitt et al. (US Pat. 3,559,652) and Collins et al.

Clark et al. (US Pat. 5,981,621), Kronenthal et al. (US Pat. 3,995,641), Hammerslag (US Pat. 6,386,203) and EP 0 965 623 are cited for the same reasons as above and are incorporated herein to avoid repetition.

Banitt et al. teaches that alkoxyalkyl 2-cyanoacrylates are biodegradable and have minimal toxicity (Column 1, lines 70-75, Column 2). It is disclosed that compared with alkyl 2-cyanoacrylates (1.2%, 9%), with the exception of methyl 2-cyanoacrylate (100% in 75 days), alkoxyalkyl 2-cyanoacrylates (34% , 54.7%, 92.3%, 100% in 16 weeks) have a substantially higher rate of absorption by living tissue (Column 6, lines 45-75, Column 7, lines 1-10).

Collins et al. teach that the longer chained alkyl cyanoacrylates, such as octyl 2-cyanoacrylate, are more effective tissue adhesives and hemostasis-inducing agents than the lower homologues because of their faster polymerization rate in blood, however, the higher homologues do not biodegrade as rapidly. (Pgs. 428, 429, 431). It is taught that the salutary combination of effectiveness in hemostasis inducing ability of the higher homologues and rapid

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biodegradation of the methyl monomer would be highly desirable in a tissue adhesive (Pgs. 431, 432).

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose a composition or film having a first monomer, which includes alkyl ester cyanoacrylate, and a different second monomer where the absorption rate of the first monomer species is different from the absorption rate of the second monomer species. However, the prior art amply suggests the same as the prior art discloses the combination of different monomers in forming medical adhesives. Further, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine an alkyl ester cyanoacrylate with higher alkyl cyanoacrylate, such as octyl 2-cyanoacrylate, with the expectation that the composition would be suitable for use as a tissue adhesive and hemostasis-inducing agent, or with an alkyl ether cyanoacrylate with the expectation that the composition would have low toxicity, and in each case, with the expectation that the biodegradation rate could be adjusted readily by modifying the ratio of the monomers. Further, one of ordinary skill in the art would have been motivated to combine sulfur dioxide and sulfuric acid with radical stabilizers such as hydroquinone, p-methoxyphenol and butylated hydroxyanisole with the expectation that the composition would be more stable. Finally, one of ordinary skill in the art would have been motivated to use benzalkonium chloride with the expectation that it would act as a polymerization initiator.

Examiner has duly considered Applicant's arguments but deems them unpersuasive, for the reasons above, to the extent that they are applicable, and the further reasons below.

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Applicant argues that neither Banitt et al. nor Collins et al. discloses selecting an alkyl ester cyanoacrylate with a cyanoacrylate in which one has a absorption rate is faster than the absorption rate of the slower absorbing species, where the difference is at least 10% or a polymerization initiator or accelerator is added comprising a quaternary amine. However, as indicated above, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 208 USPQ 871 (CCPA 1981). Banitt et al. and Kronenthal et al. disclose that the alkyl 2-cyanoacrylates, with the exception of methyl 2-cyanocrylate, have a slower absorption rate than both the alkoxyalkyl and carbalkoxyalkyl 2-cyanoacrylates, in fact greater than 10% slower. Clark et al. discloses that benzalkonium chloride is suitable for use as a polymerization initiator. Collins et al. discloses that octyl 2-cyanoacrylate polymerizes readily in blood but does not biodegrade readily which is desired. As such, one of ordinary skill in the art would be expect that combining octyl 2-cyanoacrylate with an alkoxyalkyl or carbalkoxyalkyl 2-cyanoacrylate will result in a faster biodegradation rate and that addition of the benzalkonium chloride will assist in maintaining a rapid polymerization which is also desired.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

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Claims 1, 3,4, 8, 9,11,12,14,59-62,64,66-71,73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Berger et al. (US Pat. 5,998,472) in view of Kronenthal et al. (US Pat. 3,995,641), Hammerslag (US Pat. 6,386,203) and Clark et al. (US Pat. 5,981,621).

Berger et al discloses the mixture of reactive C1 to C8 cyanoacrylate ester monomer and a C10-C12 cyanoacrylate monomer to provide enhanced flexibility of the polymer film (Column 3, lines 1-54). It is disclosed that the term "C1 to C8 alkyl cyanoacrylate compositions" refers to polymerizable formulations comprising polymerizable cyanoacrylate ester monomers (Column 4, lines 60-68). It is disclosed that polymerizable cyanoacrylate ester monomers are known in the art and are described in US Pat. No. 3,995,641 to Kronenthal et al. (Column 1, lines 30, 31, Column 5, lines 31-44).

Kronenthal et al. (US Pat. 3,995,641), Hammerslag (US Pat. 6,386,203) and Clark et al. (US Pat. 5,981,621) are cited for the same reasons as above and are incorporated herein to avoid repetition.

The difference between the prior art and the claimed invention is that the prior art does not expressly disclose combination of alkyl ester cyanocrylate and other monomer based on difference in biodegradation rate. However, the prior art amply suggests the same as the prior art discloses the combination of different monomers in forming medical adhesives. Further, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to combine an alkyl ester cyanoacrylate with a different cyanoacrylate, such as an C10-C12 alkyl cyanoacrylate, with the expectation that biodegradation of the composition could be adjusted readily by modifying the ratio of the monomers, that the composition would exhibit a low degree of inflammatory response and that the polymerized film would exhibit flexibility.

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Finally, one of ordinary skill in the art would have been motivated to use benzalkonium chloride with the expectation that it would act as a polymerization initiator.

Examiner has duly considered Applicant's arguments but deems them unpersuasive for the same reasons as above to the extent they are applicable herein. Further, contrary to Applicant's arguments the combined teachings of the prior art do disclose or suggested the claimed invention as set forth in claim 1 and claim 59. Berger et al. discloses the combination of C1-C8 alkyl cyanoacrylate esters with C10-C12 alkyl cyanoacrylate esters, including carbalkoxyalkyl 2-cyanoacrylates. Kronenthal et al. discloses that the carbalkoxyalkyl 2-cyanoacrylates have substantially greater biodegradability than the alkyl 2-cyanoacrylates. Hammerslag et al. discloses that cyanoacrylates of suitable biodegradation rate can be readily selected by one of ordinary skill in the art. Clark et al. discloses mixtures of cyanoacrylates and the use of benzalkonium chloride as a polymerization initiator. As such, it would have been well within the skill of and one ordinary skill in the art to combine C1- C8 alkyl 2-cyanoacrylates and C10-C12 carbalkoxyalkyl 2-cyanoacrylates with the expectation that both flexibility and biodegradation rate could be obtained as desired and that addition of benzalkonium chloride would be effective obtaining the desired rate of polymerization.

Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention has been collectively taught by the combined teachings of the references.

Terminal Disclaimer

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Examiner notes that Applicant is correct "6,662,846" was a typographical error.

Examiner intended US Pat. No. 6,620,846 in the double patenting rejection set forth in the prior Office Action (11/3/2004).

The terminal disclaimers filed on 4/4/2005 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Pat. Nos. 6,620,846 and 6,605,667 have been reviewed and are accepted. The terminal disclaimers have been recorded.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

A facsimile center has been established in Technology Center 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier number for accessing the facsimile machine is 571-273-8300.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Choi whose telephone number is (571)272-0610. Examiner maintains a flexible schedule. However, Examiner may generally be reached Monday-Friday, 8:00 am – 5:30 pm (EST), except the first Friday of the each biweek which is Examiner's normally scheduled day off.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Mr. Gary Kunz, can be reached at 571-272-0887. Additionally, Technology Center 1600's Receptionist and Customer Service can be reached at (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

FIC

July 18, 2005



SABIHA QAZI, PH.D
PRIMARY EXAMINER